81410292

81410292-473780001 (Rev. Oct. 2008)

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Kogenate FS safely and effectively. See full prescribing information for Kogenate FS.

Kogenate FS (Antihemophilic Factor [Recombinant] Formulated with Sucrose)
For Intravenous Use, Lyophilized Powder for Reconstitution
Initial U.S. Approval: 1993

---------- RECENT MAJOR CHANGES ----------

Indications and Usage (1.3) (10/2008)

---------- INDICATIONS AND USAGE ----------

Kogenate FS is an Antihemophilic Factor (Recombinant) indicated for:

- Control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A (1.1).
- Peri-operative management in adults and children with hemophilia A (1.2).
- Routine prophylaxis to reduce the frequency of bleeding episodes and the risk of joint damage in children with hemophilia A with no pre-existing joint damage (1.3).

---------- DOSAGE AND ADMINISTRATION ----------

For intravenous use only

- Each vial of Kogenate FS contains the labeled amount of recombinant factor VIII in international units (IU) (2).

Control and prevention of bleeding episodes and peri-operative management (2)**:**

- Dose (units) = body weight (kg) × desired factor VIII rise (IU/dL or % of normal) × 0.5 (IU/kg per IU/dL).
- Frequency of intravenous injection of the reconstituted product is determined by the type of bleeding episode and the recommendation of the treating physician (2.1, 2.2).

For routine prophylaxis in children with no pre-existing joint damage, the recommended dose is 25 IU/kg every other day (2.3).

---------- DOSAGE FORMS AND STRENGTHS ----------

- Kogenate FS powder is available as 250, 500, 1000, and 2000 IU in single use vials (3).

---------- CONTRAINDICATIONS ----------

Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins (4).

---------- WARNINGS AND PRECAUTIONS ----------

- Anaphylaxis and severe hypersensitivity reactions are possible. Should symptoms occur, treatment with Kogenate FS should be discontinued, and emergency treatment should be sought (5.2).
- Development of activity-neutralizing antibodies has been detected in patients receiving factor VIII-containing products. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed (5.3).
- Patients may develop hypersensitivity to mouse or hamster protein, which is present in trace amounts in the product (5.4).

---------- ADVERSE REACTIONS ----------

The most common adverse reactions observed in clinical trials (frequency ≥ 4% of patients) are inhibitor formation in previously untreated and minimally treated patients (PUPs and MTPs), skin associated hypersensitivity reactions (rash, pruritus, urticaria, infusion site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections.

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare at 1-888-84BAYER or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS ----------

None known.

---------- USE IN SPECIFIC POPULATION ----------

Higher factor VIII clearance has been described in children (4.4-16 years) compared to adults. Dose adjustment may be needed.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: October/2008

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Control and Prevention of Bleeding Episodes

Kogenate® FS is an antihemophilic factor that is indicated for the control and prevention of bleeding episodes in adults and children (0-16 years) with hemophilia A.

1.2 Peri-operative Management

Kogenate FS is indicated for surgical prophylaxis in adults and children with hemophilia A.

1.3 Routine Prophylaxis in Children with Hemophilia A with No Pre-existing Joint Damage

Kogenate FS is indicated for routine prophylactic treatment to reduce the frequency of bleeding episodes and the risk of joint damage in children with no pre-existing joint damage.

Kogenate FS is not indicated for the treatment of von Willebrand's disease.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use After Reconstitution

- Treatment with Kogenate FS should be initiated under the supervision of a physician experienced in the treatment of hemophilia A.
- Each vial of Kogenate FS has the rFVIII potency in international units stated on the label.
- Dosage and duration of treatment depend on the severity of the factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition.[2] Careful control of replacement therapy is especially important in cases of major surgery or life-threatening bleeding episodes. [*see Table 1 and Table 2*]

The expected in vivo peak increase in factor VIII level expressed as IU/dL (or % normal) can be estimated using the following formulas:

Dosage (units) = body weight (kg) × desired factor VIII rise (IU/dL or % or normal) × 0.5 (IU/kg per IU/dL)

OR

IU/dL (or % normal)=Total Dose (IU)/body weight (kg) × 2 [IU/dL]/[IU/kg]

Examples (assuming patient's baseline factor VIII level is <1% of normal):

1. A dose of 1750 IU Kogenate FS administered to a 70 kg patient should be expected to result in a peak post-infusion factor VIII increase of 1750 IU × {[2 IU/dL]/[IU/kg]}/[70 kg] = 50 IU/dL (50% of normal).
2. A peak level of 50% is required in a 15 kg child. In this situation, the appropriate dose would be:

   50 IU/dL/{[2 IU/dL]/[IU/kg]} × 15 kg = 375 IU.

Doses administered should be titrated to the patient's clinical response. Patients may vary in their pharmacokinetic (e.g., half-life, in vivo recovery) and clinical responses to Kogenate FS.[2, 4, 5] Although the dose can be estimated by the calculations above, it is highly recommended that, whenever possible, appropriate laboratory tests including serial factor VIII activity assays be performed. [*see 5.4 Monitoring Laboratory Tests and 12.3 Pharmacokinetics*]

2.1 Control and Prevention of Bleeding Episodes

The careful control of treatment dose is especially important in cases of life–threatening bleeding episodes or major surgery.

The following table can be used to guide dosing in bleeding episodes:

Table 1 Control and Prevention of Bleeding Episodes For Children and Adults

Type of Bleeding Episode	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Early hemarthorsis, minor muscle or oral bleeds.	20–40	10–20 IU per kg Repeat dose if there is evidence of further bleeding.
Moderate Bleeding into muscles, bleeding into the oral cavity, definite hemarthroses, and known trauma.	30–60	15–30 IU per kg Repeat dose every 12–24 hours until bleeding is resolved.
Major Gastrointestinal bleeding. Intra-cranial, intra-abdominal or intra-thoracic bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath. Fractures. Head trauma.	80–100	Initial dose 40–50 IU per kg Repeat dose 20–25 IU per kg every 8–12 hours until bleeding is resolved.

2.2 Peri-operative Management

The careful control of treatment dose is especially important in cases of major surgery or life-threatening bleeding episodes.

The following table can be used to guide dosing in surgery:

Table 2 Peri-operative Management for Adults and Children

Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Dosage and Frequency Necessary to Maintain the Therapeutic Plasma Level
Minor Including tooth extraction	30–60	15–30 IU per kg Repeat dose every 12–24 hours until bleeding is resolved.
Major Examples include tonsillectomy, inguinal herniotomy, synovectomy, total knee replacement, craniotomy, osteo-synthesis, trauma	100	Pre-operative dose 50 IU per kg Verify 100% activity prior to surgery. Repeat as necessary after 6 to 12 hours initially, and for 10 to 14 days until healing is complete.

2.3 Routine Prophylaxis in Children with No Pre-existing Joint Damage.[6,7]

The recommended dose for routine prophylaxis is 25 IU/kg of body weight every other day.[7]

2.4 Instructions for Use

Kogenate FS is administered by intravenous (IV) injection after reconstitution. Patients should follow the specific reconstitution and administration procedures provided by their physicians.

For instructions, patients should follow the recommendations in the FDA Approved Patient Labeling. [*see 17.1 FDA-Approved Patient Labeling*]

Reconstitution, product administration, and handling of the administration set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted Kogenate FS product, in an appropriate container.

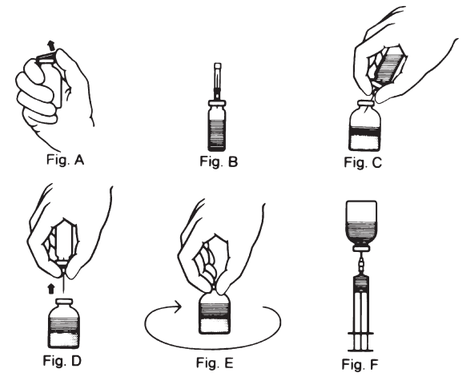
2.5 Preparation and Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of Kogenate FS.

Always work on a clean surface and wash your hands before performing the following procedures.

Vacuum Transfer and Reconstitution

1. Warm the unopened diluent and the concentrate to a temperature not to exceed 37°C, 99°F.
2. After removing the plastic flip top caps (Fig. A), aseptically cleanse the rubber stoppers of both vials with alcohol, being careful not to handle the rubber stopper.
3. Remove the protective cover from *one end* of the plastic transfer needle cartridge and penetrate the stopper of the diluent vial (Fig. B).
4. Remove the remaining portion of the *protective cover*, invert the diluent vial and penetrate the rubber seal on the concentrate vial (Fig. C) with the needle at an angle.
5. The vacuum will draw the diluent into the concentrate vial. Hold the diluent vial at an angle to the concentrate vial in order to direct the jet of diluent against the wall of the concentrate vial (Fig. C). Avoid excessive foaming. If the diluent does not get drawn into the vial, there is insufficient vacuum and the product should not be used.
6. After removing the diluent vial and transfer needle (Fig. D), swirl until completely dissolved without creating excessive foaming (Fig. E).
7. Re-swab top of reconstituted Kogenate FS vial with alcohol. Allow the stopper to air dry.
8. After the concentrate powder is completely dissolved, withdraw the solution into the syringe through the filter needle that is supplied in the package (Fig. F). Replace the filter needle with the administration set provided and inject intravenously. NOTE: See accompanying instructions for Infusion Set with Filter.
9. If the same patient is to receive more than one vial, the contents of two vials may be drawn into the same syringe through a separate unused filter needle before attaching the vein needle.
10. Kogenate FS should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.



2.6 Administration

For Intravenous Use Only After Reconstitution

- Kogenate FS should be inspected visually for particulate matter and discoloration prior to administration, wherever solution and container permit. Turbid or discolored solution should be discarded.
- Reconstituted Kogenate FS may be stored at room temperature prior to administration, but is to be administered within 3 hours. It is recommended to use the IV administration set provided.
- A dose of Kogenate FS may be administered over a period of 1 to 15 minutes. The rate of administration however, should be adapted to the response of each individual patient. The pulse rate should be determined before and during administration of Kogenate FS. If there is a significant increase in pulse rate, reducing the rate of administration or temporarily halting the injection allows the symptoms to disappear promptly.

3 DOSAGE FORMS AND STRENGTHS

Kogenate FS is available as a lyophilized powder in single use glass vials containing 250, 500, 1000, and 2000 International Units (IU).

Each vial of Kogenate FS is labeled with the recombinant antihemophilic factor activity expressed in IU per vial. This potency assignment employs a factor VIII concentrate standard that is referenced to a WHO International Standard for factor VIII concentrates, and is evaluated by appropriate methodology to ensure accuracy of the results.

4 CONTRAINDICATIONS

Kogenate FS is contraindicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including mouse or hamster proteins.

5 WARNINGS AND PRECAUTIONS

5.1 General

The clinical response to Kogenate FS may vary. If bleeding is not controlled with the recommended dose, the plasma level of factor VIII should be determined and a sufficient dose of Kogenate FS should be administered to achieve a satisfactory clinical response. If the patient's plasma factor VIII level fails to increase as expected or if bleeding is not controlled after the expected dose, the presence of an inhibitor (neutralizing antibodies) should be suspected and appropriate testing performed. [*see 5.4 Monitoring Laboratory Tests*]

5.2 Anaphylaxis and Severe Hypersensitivity Reactions

Allergic-type hypersensitivity reactions including anaphylaxis have been reported with Kogenate FS and have manifested as pruritus, rash, urticaria, hives, facial swelling, dizziness, hypotension, nausea, chest discomfort, cough, dyspnea, wheezing, flushing, discomfort (generalized) and fatigue. Discontinue Kogenate FS if symptoms occur and seek immediate emergency treatment.

Kogenate FS contains trace amounts of mouse immunoglobulin G (MuIgG) and hamster (BHK) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

5.3 Neutralizing Antibodies

Patients treated with antihemophilic factor (AHF) products should be carefully monitored for the development of factor VIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of Kogenate FS predominantly in previously untreated patients. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor VIII inhibitor concentration should be performed. [*see 5.4 Monitoring Laboratory Tests*]

5.4 Monitoring Laboratory Tests

- Monitor plasma factor VIII activity levels monitored by the one-stage clotting assay to confirm the adequate factor VIII levels have been achieved and maintained, when clinically indicated. [*see 2 Dosage and Administration*]
- Monitor for development of factor VIII inhibitors. Perform assay to determine if factor VIII inhibitor is present if expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with the expected dose of Kogenate FS. Use Bethesda Units (BU) to titer inhibitors.
  - If the inhibitor is less than 10 BU per mL, the administration of additional Kogenate FS concentrate may neutralize the inhibitor, and may permit an appropriate hemostatic response.
  - Adequate hemostasis may not be achieved if Inhibitor titers are above 10 BU per mL. The inhibitor titer may rise following Kogenate FS infusion as a result of an anamnestic response to factor VIII. The treatment or prevention of bleeding in such patients requires the use of alternative therapeutic approaches and agents.

6 ADVERSE REACTIONS

The most serious adverse reactions are systemic hypersensitivity reactions including bronchospastic reactions and/or hypotension and anaphylaxis and the development of high-titer inhibitors necessitating alternative treatments to AHF.

The most common adverse reactions observed in clinical trials (frequency ≥ 4% of patients) are inhibitor formation in PUPs and MTPs, skin-related hypersensitivity reactions (e.g., rash, pruritus), infusion site reactions (e.g., inflammation, pain), and central venous access device (CVAD) line-associated infections in patients requiring a CVAD for intravenous administration.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

Previously Treated Patients (PTPs)

During the clinical studies conducted in PTPs, 451 adverse events, (irrespective of the relationship to the study drug) were reported in the course of 24,936 infusions (1.8%). Twenty-four of the 451 adverse events were assessed as related to Kogenate FS (0.1%).

Adverse reactions reported by ≥ 4% of the patients are listed in Table 3 below.

Table 3 Adverse Reactions (AR) in Previously Treated Patients (PTPs) with Frequency of ≥ 4%

MedDRA Primary SOC	Preferred Term	Total No. of Patients: 73 No. of Patients with AR (%)	Total No. of Infusions: 24,936 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus	6 (8.2%)	0.02
General Disorders and Administration Site Conditions	Infusion site reactions	3 (4.1%)	0.01

SOC = System Organ Class

Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs)

In clinical studies with PUPs and MTP pediatric patients, 726 adverse events were reported in the course of 9,389 infusions (7.7%). Twenty-nine of the 726 adverse events were assessed as related to Kogenate FS (0.3%).

Adverse reactions reported by ≥ 4% of the patients are listed in Table 4 below.

Table 4 Adverse Reactions (AR) in Previously Untreated Patients (PUPs) and Minimally Treated Patients (MTPs) with Frequency of ≥ 4% (Age Range 2-27 months)

MedDRA Primary SOC	Preferred Term	Total No. of Patients: 61 No. of Patients with AR (%)	Total No. of Infusions: 9,389 AR per Infusion (%)
Skin and Subcutaneous Tissue Disorders	Rash, pruritus,urticaria	10 (16.4)	0.01
Blood and Lymphatic System Disorders	Factor VIII inhibition	9 (15)*	N/A
General Disorders and Administration Site Conditions	Infusion site reactions	4 (6.6)	0.04

SOC = System Organ Class

*Denominator for de-novo inhibitors is N=60, since one patient had a pre-existing inhibitor.

Minimally Treated Patients (MTPs) in the Joint Outcome Study

In the Joint Outcome Study in MTP pediatric patients treated with routine prophylaxis or episodic enhanced treatment for 5.5 years, 46 of the 65 randomized patients experienced adverse events over the study duration. Adverse events were not assessed for their relationship with Kogenate FS.

Table 5 Adverse Events (AE) in MTPs in the Joint Outcome Study (Age Range 0-6 years)

MedDRA Primary SOC	Preferred Term	Total No. of Prophylaxis Arm Patients: 32 No. of Patients with AE (%)	Total No. of Enhanced Episodic Arm Patients: 33 No. of Patients with AE (%)
Surgical and Medical Procedures	Central venous catheterization, Catheter removal	19 (59)	18* (55)
Infections and Infestations	Central line infection	6 (19)	6 (18)
General Disorders and Administration Site Conditions	Pyrexia	1 (3)	4 (12)

SOC = System Organ Class

*Three patients from the enhanced episode arm had catheter removal.

Kogenate FS contains trace amounts of mouse and hamster proteins. Patients treated with this product could develop hypersensitivity to these non-human mammalian proteins [*see 5.2 Anaphylaxis and Severe Hypersensitivity Reactions*]. No adverse events associated with such proteins have been reported in controlled clinical trials.[11 12]

Immunogenicity

In clinical studies with 73 PTPs (defined as having more than 100 exposure days), one patient had a pre-existing inhibitor. In the other 72 patients, followed over 4 years, no de-novo inhibitors were observed.

In clinical studies with pediatric PUPs and MTPs, inhibitor development was observed in 9 out of 60 patients (15%), 6 were high titer[2] (>5 BU) and 3 were low-titer inhibitors. Inhibitors were detected at a median number of 7 exposure days (range 2 to 16 exposure days).

In the pediatric prophylaxis clinical trial with Kogenate FS,[7] de-novo inhibitor development was observed in 8 of 64 patients with negative baseline values (12.5%), 2 patients developed high titer[2] (>5 BU) and were withdrawn from the study. Six patients developed low-titer inhibitors. Inhibitors were detected at a median number of 44 exposure days (range 5 to 151 exposure days).

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post approval use of Kogenate FS. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Among patients treated with Kogenate FS, cases of serious allergic/hypersensitivity reactions (which may include facial swelling, flushing, hives, blood pressure decrease, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, vomiting) have been reported, particularly in very young patients or patients who have previously reacted to other factor VIII concentrates.

The following table represents the post-marketing adverse reactions as MedDRA Preferred Terms.

Table 6 Post-Marketing Experience

MedDRA Primary SOC	Preferred Term
Blood and Lymphatic System Disorders	FVIII inhibition
Skin and Subcutaneous Tissue Disorders	Pruritus, urticaria, rash
General Disorders and Administration Site Conditions	Infusion site reaction
	Pyrexia
Immune System Disorders	Anaphylactic reaction, other hypersensitivity signs and symptoms

SOC = System Organ Class

7 DRUG INTERACTIONS

None known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Kogenate FS. It is also not known whether Kogenate FS can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Kogenate FS should be used during pregnancy only if clinically needed.

8.2 Labor and Delivery

There is no information available on the effect of factor VIII replacement therapy on labor and delivery. Kogenate FS should be used only if clinically needed.

8.3 Nursing Mother

It is not known whether this drug is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if Kogenate FS is administered to nursing mothers. Kogenate FS should be given to nursing mothers only if clinically needed.

8.4 Pediatric Use

Safety and efficacy studies have been performed in previously untreated and minimally treated pediatric patients. Children in comparison to adults present higher factor VIII clearance values and thus lower recovery of factor VIII. This may be explained by differences in body composition[13] and should be taken into account when dosing or following factor VIII levels in such a population. [*see 12.3 Pharmacokinetics*] Routine prophylactic treatment in children ages 0-2.5 years with no pre-existing joint damage has been shown to reduce spontaneous joint bleeding and the risk of joint damage. This data can be extrapolated to ages >2.5-16 years for children who have no existing joint damage. [*see 14 Clinical Studies*]

8.5 Geriatric Use

Clinical studies with Kogenate FS did not include patients aged 65 and over. Dose selection for an elderly patient should be individualized.

11 DESCRIPTION

Kogenate FS Antihemophilic Factor (Recombinant) is a coagulation factor VIII produced by recombinant DNA technology. It is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII gene has been introduced.[14] The cell culture medium contains Human Plasma Protein Solution (HPPS) and recombinant insulin, but does not contain any proteins derived from animal sources. Kogenate FS is a highly purified glycoprotein consisting of multiple peptides including an 80 kD and various extensions of the 90 kD subunit. It has the same biological activity as factor VIII derived from human plasma. No human or animal proteins, such as albumin, are added during the purification and formulation processes of Kogenate FS.

The purification process includes a solvent/detergent virus inactivation step in addition to the use of the purification methods of ion exchange chromatography, monoclonal antibody immunoaffinity chromatography, along with other chromatographic steps designed to purify recombinant factor VIII and remove contaminating substances.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the vCJD and CJD agents.[15-27] Several of the individual production and raw material preparation steps in the Kogenate FS manufacturing process have been shown to decrease TSE infectivity of that experimental model agent. TSE reduction steps include the Fraction II+III separation step for HPPS (6.0 $\log_{10}$) and an anion exchange chromatography step (3.6 $\log_{10}$).

Kogenate FS is formulated with the following as stabilizers [*see Table 7*] in the final container and is then lyophilized. The final product is a sterile, nonpyrogenic, preservative-free, powder preparation for intravenous (IV) injection. Intravenous administration of sucrose contained in Kogenate FS will not affect blood glucose levels.

Table 7 Stabilizers Contained in Kogenate FS Final Container

Stablilizer	250 IU, 500 IU, 1000 IU	2000 IU
Sucrose	0.9–1.3%	0.9–1.2%
Glycine	21–25 mg/mL	20–24 mg/mL
Histidine	18–23 mmol/L	17–22 mmol/L

The following inactive ingredients/excipients are also contained in the final product:

Table 8 Inactive Ingredients/Excipients

Inactive Ingredient/Excipient	250 IU, 500 IU, 1000 IU	2000 IU
Sodium	27–36 mEq/L	26–34 mEq/L
Calcium	2.0–3.0 mmol/L	1.9–2.9 mmol/L
Chloride	32–40 mEq/L	31–38 mEq/L
Polysorbate 80	64–96 µg/mL	64–96 µg/mL
Sucrose	28 mg/vial	52 mg/vial
Imidazole,tri-n-butyl phosphate, and copper	Trace amounts	Trace amounts

Each vial of Kogenate FS contains the labeled amount of recombinant factor VIII in international units (IU). One IU, as defined by the World Health Organization standard for blood coagulation factor VIII, human, is approximately equal to the level of factor VIII activity found in 1 mL of fresh pooled human plasma.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Kogenate FS temporarily replaces the missing clotting factor VIII that is needed for effective hemostasis.

12.2 Pharmacodynamics

The aPTT is prolonged in patients with hemophilia. Determination of activated partial thromboplastin time (aPTT) is a conventional in vitro assay for biological activity of factor VIII. Treatment with Kogenate FS normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

The pharmacokinetic properties of Kogenate FS were investigated in two separate studies in previously treated patients, adults and children.

Pharmacokinetic studies with Kogenate FS were conducted in 20 PTPs (ages 12 to 33) with severe hemophilia A in North America. The pharmacokinetic parameters for Kogenate FS were measured in a randomized, crossover clinical trial with the predecessor KOGENATE product with a single dose administration of 50 IU/kg. After 24 weeks, the same dose of Kogenate FS was administered to the same patients. The recovery and half-life data for Kogenate FS were unchanged after 24 weeks of continued treatment with sustained efficacy and no evidence of factor VIII inhibition. [*see Table 9*]

Table 9 Pharmacokinetic Parameters for Kogenate FS Compared to KOGENATE

Parameter	Kogenate FS		KOGENATE
	Initial PK Mean (±SD)	PK at week 24 Mean (±SD)	Reference Mean (±SD)
AUC (IU • h/dL)	1588.05 ±344.32	1487.08 ±381.73	1879.02 ±412.32
Cmax (IU/dL)	114.95 ±20.19	109.42 ±20.09	127.40 ±33.21
Half-life (hr)	13.74 ±1.82	14.60 ±4.38	14.07 ±2.62
In Vivo Recovery (IU/dL / IU/kg)	2.20 ±0.34	2.11 ±0.37	2.43 ±0.60

The pharmacokinetics of Kogenate FS were investigated in pediatric PTPs (4.4-18.1 years of age, average age 12).[13] The pharmacokinetic parameters in children compared to adults show differences in higher clearance, lower incremental in vivo factor VIII recovery and a shorter factor VIII half-life. This might be explained by differences in body composition such as body surface area and plasma volume. The pharmacokinetic parameters are depicted in Table 10.

Table 10 Pharmacokinetic Parameters for Kogenate FS in Children

Parameter	Mean (range)
AUC (IU • h/dL)	1320.0
Clearance (mL/h•kg)	4.1
Half-life (hr)	10.7 (7.8–15.3)
In Vivo Recovery (IU/dL / IU/kg)	1.9 (1.25–2.76)

13 NONCLINICAL TOXICOLOGY

Preclinical studies evaluating Kogenate FS in hemophilia A with mice, rats, rabbits, and dogs demonstrated safe and effective restoration of hemostasis. Doses several fold higher than the recommended clinical dose (related to body weight) did not demonstrate any acute or subacute toxic effect for Kogenate FS in laboratory animals.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted with Kogenate FS to assess its mutagenic or carcinogenic potential and impairment of fertility. Kogenate FS has been shown to be comparable to the predecessor product with respect to its biochemical and physio-chemical properties, as well as its non-clinical in vivo pharmacology and toxicology. By inference, the predecessor product and Kogenate FS would be expected to have equivalent mutagenic and carcinogenic potential.

The predecessor product did not demonstrate reverse mutation or chromosomal aberrations at doses substantially greater than the maximum expected clinical dose. In vivo evaluation with the predecessor product in animals using doses ranging between 10 and 40 times the expected clinical maximum also indicated that the predecessor product did not possess a mutagenic potential. Long-term investigations of carcinogenic potential in animals have not been performed due to the immune response to heterologous proteins in all non-human mammalian species.

14 CLINICAL STUDIES

14.1 Previously Treated Patients (PTPs)

A total of 73 patients with severe (≤ 2% FVIII) hemophilia A, ages 12–59, who had been previously treated with other recombinant or with plasma-derived AHF products, were treated up to 54-months in open label studies with Kogenate FS in Europe and North America. A total of 5,684 bleeding episodes were treated during the study. Patients could be treated on demand or on prophylaxis. Regularly scheduled prophylaxis treatment represented 76% of all infusions (treatment regimens of 2-3 infusions per week). [*see Table 11*]

Table 11 Previously Treated Patients (PTPs) Clinical Trial Results

Clinical Parameters	Results
No. of Infusions of Kogenate FS Administered	24,924
No. of IU Administered	45 million IU
No. of Bleeds Treated with Kogenate FS	5,684
Percentage of Bleeds Treated with One or Two Infusions of Kogenate FS	one infusion: 79.7% two infusions: 13.0% total: 92.7%
Mean Kogenate FS Dose per Treatment Infusion (in Europe and North America, respectively)	Approximately 32.5 and 29.6 IU/kg per treatment infusion

A total of 31 patients received Kogenate FS for 43 surgical procedures during the PTP study. There were both minor and major surgery types, 27 and 16 respectively. The surgeon or treating physician assigned a rating to the hemostatic outcome according to 4 categories; "excellent," "good," "moderate," or "none." Hemostasis was rated as satisfactory ("excellent" or "good") in all cases. [*see Table 13*]

14.2 Previously Untreated and Minimally Treated Patients (PUPs and MTPs)

Kogenate FS has been used in the treatment of bleeding episodes in previously untreated patients (PUPs) and minimally treated (MTP) pediatric patients with severe (< 2% FVIII) hemophilia A. There were 37 PUPs and 24 MTPs (defined as having equal to or less than 4 exposure days) treated with a total of 9,419 infusions of Kogenate FS for a follow up duration up to 3.1 years. A total of 1047 bleeding episodes were treated.

Table 12 Previously Untreated and Minimally Treated Patients (PUPs and MTPs) Clinical Trial Results

Clinical Parameters	Results
No. of Infusions of Kogenate FS Administered	9,419
No. of Exposure Days to Kogenate FS (median)	115 exposure days
No. of IU Administered	7.5 million IU
No. of Bleeds Treated with Kogenate FS	1,047
Percentage of Bleeds Treated with One or Two Infusions of Kogenate FS	one infusion 73.1% two infusions 15.0% total: 88.1%

A total of 29 surgical procedures were performed in 23 patients during the PUPs and MTPs study. There were both minor and major surgery types, 23 and 6 respectively. The surgeon or treating physician assigned a rating to the hemostatic outcome according to 4 categories; "excellent," "good," "moderate," or "none." Hemostasis was rated as satisfactory ("excellent" or "good") in all cases. [*see Table 13*]

Table 13 Surgical Procedures Performed During PTP and PUP/MTP Clinical Trials

Type of Surgery	PTPs (N=31)		PUPs/MTPs (N=23)	
	No. of Surgical Events	Outcome "Good" or "Excellent"	No. of Surgical Events	Outcome "Good" or "Excellent"
Minor Surgery (i.e., tooth extractions, catheter implantations, liver biopsies)	24	100%	21	100%
Major Surgery (i.e., joint replacements, craniotomies, gastro-intestinal resection)	16	100%	6	100%
Total	43		29	

14.3 Pediatric Prophylaxis and Joint Damage Risk Reduction[7]

A total of 65 boys less than 30 months of age with severe hemophilia A (FVIII level ≤ 2 IU/dL) and with ≤ 2 bleeds into each index joint and normal baseline joint imaging, were observed for up to 5.5 years in a multicenter, open-label, prospective, randomized, controlled clinical study. Patients received either 25 IU/kg every other day (primary prophylaxis; n=32) or at least 3 doses totaling a minimum of 80 IU/kg at the time of a bleeding episode (enhanced episodic; n=33). Joint damage was evaluated by magnetic resonance imaging (MRI) or radiography, as well as the frequency of bleeding episodes. Joint damage detected by MRI or radiography in the ankles, knees, and elbows (i.e., index joints) was statistically significantly lower (p=0.002) for subjects receiving prophylactic therapy (7%) than for subjects receiving episodic therapy (42%). This corresponds to a 6.29-fold relative risk of joint damage for subjects treated with enhanced episodic therapy compared to prophylaxis. The mean rate of index joint hemorrhages for subjects on episodic therapy was 4.89 bleeds per year, versus 0.63 bleeds per year observed in the prophylaxis arm. Ten percent (10%) of subjects in the episodic arm experienced recurrent life threatening bleeds (intracranial, gastrointestinal) compared to no subjects in the prophylaxis arm. On a per joint basis, joints in the regular prophylaxis arm were nearly 8-fold more likely to remain damage-free than those in the episodic arm. Joint damage was most frequently observed in ankle joints and was detected at higher rates by MRI than by radiography. Ankles were also the index joint that demonstrated the highest frequency of bleeding events in this study (left ankle, mean 2.7 hemorrhages; right ankle, mean 2.6 hemorrhages).

As shown in Table 14 below, the incidence of joint damage was statistically significantly lower in the prophylactic group as compared to the episodic treatment group when assessed by MRI, or either MRI or radiography, using predefined criteria (described below) for establishing joint damage. However, there was no statistically significant difference between the two groups when joint damage was assessed by radiography alone.

To evaluate joint damage, MRIs were scored using a scale developed by Nuss et al.[28] and X-rays were scored using the method of Pettersson et al.[29] Both the scales have been validated in various clinical trials and are routinely used for joint damage evaluation in hemophiliacs. Joint damage was defined as bone and/or cartilage damage including subchondral cysts, erosions and cartilage loss with narrowing of joint space. This corresponded to a total MRI score of ≥ 7 or an X-ray score of ≥ 1 in any of the following categories: subchondral cysts, erosions of joint surfaces or narrowing of joint spaces. Images were read separately by two independent radiologists centrally. Any discrepant reading was read by an independent third radiologist who was not aware of the initial reading results. The concordant reading of two out of three readers was used for analysis purposes.

Table 14 Subjects with Joint Damage (Subjects with Available Baseline and Endpoint Data)

Endpoint Assessment	Prophylaxis		Episodic Therapy		p-value
	Incidence (%)	Relative Risk (95% CI)	Incidence (%)	Relative Risk (95% CI)	
MRI	2/27 (7%)	0.17 (0.04, 0.67)	13/29 (45%)	6.05 (1.50, 24.38)	0.002
Radiography	1/28 (4%)	0.19 (0.02, 1.55)	5/27 (19%)	5.19 (0.65, 41.54)	0.101
MRI or Radiography	2/30 (7%)	0.16 (0.04, 0.65)	13/31 (42%)	6.29 (1.55, 25.55)	0.002

Relative Risk is the risk of damage to one or more index joints on the given therapy as compared to the other therapy.

P-value is from the 2-sided Fisher Exact Test comparing the incidence of joint damage between treatment groups.

As shown in the Table 15 below, the assessment of endpoints in all randomized subjects assuming that those without complete baseline and endpoint data are treatment failures (intention-to-treat analysis). The incidence of joint damage was statistically significantly lower in the prophylactic group as compared to the episodic treatment group, with similar p-values, when assessed by MRI, or either MRI or radiography.

Table 15 Subjects with Joint Damage (All Randomized Subjects Assuming Subjects without Complete Baseline and Endpoint Data as Treatment Failures)

Endpoint Assessment	Prophylaxis (n=32)		Episodic Therapy (n=33)		p-value
	Incidence (%)	Relative Risk (95% CI)	Incidence (%)	Relative Risk (95% CI)	
MRI	7 (22%)	0.42 (0.20, 0.88)	17 (52%)	2.35 (1.13, 4.90)	0.020
Radiography	5 (16%)	0.47 (0.18, 1.20)	11 (33%)	2.13 (0.83, 5.45)	0.150
MRI or Radiography	8 (25%)	0.43 (0.22, 0.85)	19 (58%)	2.3 (1.18, 4.49)	0.012

Relative Risk is the risk of damage to one or more index joints on the given therapy as compared to the other therapy.

P-value is from the 2-sided Fisher Exact Test comparing the incidence of joint damage between treatment groups.

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Kogenate FS is available as a kit in the following single use glass vials. A suitable volume of Sterile Water for Injection, USP, a double-ended transfer needle, a filter needle, and an administration set are provided in the kit.

NDC Number	Approximate FVIII Activity (IU)	Diluent (mL)
0026-3782-20	250	2.5
0026-3783-30	500	2.5
0026-3785-50	1000	2.5
0026-3786-60	2000	5.0

Actual factor VIII activity in IU is stated on the label of each Kogenate FS Vial.

16.2 Storage and Handling

Product as Packaged for Sale:

- Kogenate FS should be stored under refrigeration (2–8°C; 36–46°F).
- Storage of lyophilized powder at room temperature (up to 25°C or 77°F) for 3 months, such as in home treatment situations, may be done. If Kogenate FS is stored outside the refrigerator, please add the date removed from refrigeration and note a new expiry date on the carton and vial. The new expiry date should be 3 months from the date product is removed from the refrigerator, or the previously stamped expiry date, whichever is shorter.
- Once Kogenate FS is removed from refrigeration, it cannot be returned to the refrigerator.
- Do not use Kogenate FS after the expiration date indicated on the vial.
- Do not freeze.
- Protect from extreme exposure to light and store the lyophilized powder in the carton prior to use.

Product After Reconstitution:

Administer Kogenate FS within 3 hours after reconstitution.

It is recommended to use the administration set provided.

17 PATIENT COUNSELING INFORMATION

See Patient Product Information (PPI) and Instructions for Use

Advise patients to report any adverse reactions or problems following Kogenate FS administration to their physician or healthcare provider.

- Allergic-type hypersensitivity reactions have been reported with Kogenate FS. Warn patients of the early signs of hypersensitivity reactions [including hives (rash with itching), generalized urticaria, tightness of the chest, wheezing, hypotension] and anaphylaxis. Advise patients to discontinue use of the product if these symptoms occur and seek immediate emergency treatment with resuscitative measures such as the administration of epinephrine and oxygen.
- In clinical studies with Kogenate FS, a 15% incidence of inhibitor development was observed in PUPs/MTPs and zero de-novo inhibitors were observed with the PTPs. Inhibitor formation may occur at any time in the treatment of a patient with hemophilia A. Advise patients to contact their physician or treatment center for further treatment and/or assessment, if they experience a lack of clinical response to factor VIII replacement therapy, as this may be a manifestation of an inhibitor.
- Advise patients to consult with their healthcare provider prior to travel. While traveling advise patients to bring an adequate supply of Kogenate FS based on their current regimen of treatment.

17.1 FDA-Approved Patient Labeling – Patient Product Information (PPI)

Kogenate FS (kō-jen-ate) Antihemophilic Factor (Recombinant) Formulated with Sucrose

This leaflet summarizes important information about Kogenate FS. Please read it carefully before using this medicine. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about Kogenate FS. If you have any questions after reading this, ask your healthcare provider.

Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.

What is Kogenate FS?

Kogenate FS is a medicine used to replace clotting factor (factor VIII or antihemophilic factor) that is missing in people with hemophilia A (also called "classic" hemophilia). Hemophilia A is an inherited bleeding disorder that prevents blood from clotting normally.

Kogenate FS is used to prevent and control bleeding in adults and children (0-16 years) with hemophilia A. Your healthcare provider may give you Kogenate FS when you have surgery. Kogenate FS can reduce the number of bleeding episodes when used regularly and reduce the risk of joint damage in children.

Kogenate FS is not used to treat von Willebrand's Disease.

Who should not use Kogenate FS?

You should not use Kogenate FS if you

- are allergic to rodents (like mice and hamsters).
- are allergic to any ingredients in Kogenate FS, such as; polysorbate 80, imidazole, or tri-n-butyl phosphate.

Tell your healthcare provider if you are pregnant or breast-feeding because Kogenate FS may not be right for you.

What should I tell my healthcare provider before I use Kogenate FS?

Tell your healthcare provider about all of your medical conditions.

Tell your healthcare provider and pharmacist about all of the medicines you take, including all prescription and non-prescription medicines, such as over-the-counter medicines, supplements, or herbal remedies.

Tell your healthcare provider if you have been told that you have inhibitors to factor VIII (because Kogenate FS may not work for you)

What are the possible side effects of Kogenate FS?

You could have an allergic reaction to Kogenate FS. Call your healthcare provider right away and stop treatment if you get

- rash or hives
- itching
- tightness of the chest or throat
- difficulty breathing
- light-headed, dizziness
- nausea
- decrease in blood pressure

Your body can also make antibodies, called "inhibitors," against Kogenate FS, which may stop Kogenate FS from working properly. Consult with your healthcare provider to make sure you are carefully monitored with blood tests for the development of inhibitors to factor VIII.

Other common side effects with Kogenate FS include local reactions (irritation, pain, and swelling at infusion site) and injection device-related infections. Finding veins for injections may be difficult in young children. When frequent injections are required your child's healthcare provider may propose to have a device surgically placed under the skin to facilitate access to the bloodstream. These devices may result in infections. Tell your healthcare provider about any side effect that bothers you or that does not go away.

These are not all the possible side effects with Kogenate FS.

You can ask your healthcare provider for information that is written for healthcare professionals.

How do I store Kogenate FS?

Do not freeze Kogenate FS.

Kogenate FS vials containing powdered product (without sterile diluent added) should be stored in a refrigerator (2ºC–8ºC [36ºF–46ºF]), or at room temperature (up to 25ºC or 77ºF) for up to 3 months.

If you choose to store Kogenate FS at room temperature, be sure to note on the carton the date that the product is removed from refrigeration. Store vials in their original carton and protect them from extreme exposure to light.

Reconstituted product (after mixing dry products with wet diluent) must be used within 3 hours and cannot be stored.

Throw away any unused Kogenate FS after the expiration date.

Do not use reconstituted Kogenate FS if it is not clear to slightly cloudy and colorless.

What else should I know about Kogenate FS and hemophilia A?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use Kogenate FS for a condition for which it is not prescribed. Do not share Kogenate FS with other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about Kogenate FS. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about Kogenate FS that was written for healthcare professionals.

Instructions for use

How should I take Kogenate FS?

Do not attempt to self-infuse unless you have been taught how by your healthcare provider or hemophilia center.

See the step-by-step instructions for reconstituting Kogenate FS at the end of this leaflet and the specific infusion instruction leaflet provided.

You should always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using Kogenate FS. If you are unsure of the procedures, please call your healthcare provider before using.

Call your healthcare provider right away if bleeding is not controlled after using Kogenate FS.

Your healthcare provider will prescribe the dose that you should take.

Your healthcare provider may need to take blood tests from time to time.

Talk to your healthcare provider before traveling. You should plan to bring enough Kogenate FS for your treatment during this time.

Carefully handle Kogenate FS Antihemophilic Factor. Dispose of all materials, including any leftover reconstituted Kogenate FS product, in an appropriate container.

Reconstitution and use of Kogenate FS

Always work on a clean surface and wash your hands before performing the following procedures:

1. Warm the unopened diluent and the concentrate to a temperature not to exceed 37ºC, 99ºF.
2. After removing the plastic flip-top caps (Fig. A), clean the rubber stoppers of both bottles with alcohol wipes. Be careful not to handle the rubber stopper.

Fig. A

3. Remove the cover from one end of the plastic transfer needle cartridge and insert into the stopper of the diluent bottle (Fig. B).

Fig. B

4. Remove the rest of the cover from the needle cartridge. Turn over the diluent bottle. With the needle at an angle, insert into the rubber seal on the concentrate bottle (Fig. C).
5. The vacuum will suck the diluent into the concentrate bottle. Hold the diluent bottle at an angle to the concentrate bottle in order to direct the stream of diluent against the wall of the concentrate bottle (Fig. C). Avoid too much foaming. If the diluent does not get into the bottle, the product should not be used.

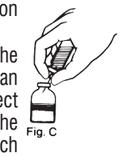
Fig. C

6. Remove the diluent bottle and transfer needle (Fig. D). Gently, swirl the bottle until the Kogenate FS infusion liquid is dissolved. Be careful not to create foam (Fig. E). Throw away any liquid that is cloudy, the wrong color, or contains particles.

Fig. D

Fig. E

7. Clean the stopper of the Kogenate FS infusion liquid bottle with an alcohol wipe. Allow the stopper to air dry.
8. Using the filter needle from the infusion set, suck the infusion liquid into the syringe (Fig. F). Replace the filter needle with the vein needle from the infusion set and follow the specific instructions for infusion provided in the accompanying infusion set leaflet.

Fig. F

9. If the same patient is getting more than one bottle for an infusion, the contents of two infusion liquid bottles can be sucked into the same syringe using separate unused filter needles before attaching the vein needle.

Rate of administration

The entire dose of Kogenate FS can usually be infused within 1 to 15 minutes. However, your healthcare provider will determine the rate of administration that is best for you.

Resources at Bayer available to the patient:

For Adverse Reaction Reporting contact:
Bayer Medical Communications 1-888-84-BAYER
(1-888-842-2937)

Contact Bayer to receive more product information:
Kogenate FS Customer Service 1-888-606-3780
Bayer Reimbursement HELPline 1-800-288-8374
For more information, visit www.kogenatefs.com

Bayer HealthCare

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Revised: October/2008

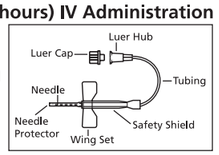
CE 0459 Non-Pyrogenic

BD Safety-Lok™

Infusion Set with Filter

For Short Term (up to 2 hours) IV Administration

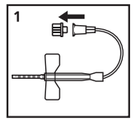
Note:
- Do not use if blister pack is open or damaged.
- IV Infusion to be performed by instructed user.

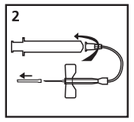


English

Directions For Use:

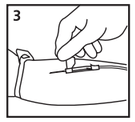
- Remove luer cap (fig. 1).
- Attach IV line or syringe to the luer hub (fig. 2).
- Remove needle protector (fig. 2).
- Prime Infusion Set in accordance with recommended procedure.

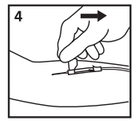




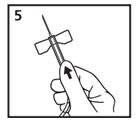
Priming Volume		
Gauge	**Microbore Tubing (inch)**	**Volume**
25	**12**	**0.22ml (220µL)**

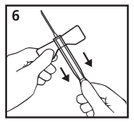
- Place tourniquet and perform venipuncture by holding wings (fig. 3).
  Do not grasp the safety shield to place needle in vein.
- Remove tourniquet before administering medication.
- Withdraw needle from vein by: (fig. 4)
  - Grasping the wing set with the thumb and index finger while at the same time grasping the tubing, or
  - Grasping either one wing or both wings of wing set and withdraw.

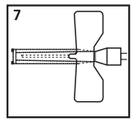




- Activate the safety shield feature (as shown in fig. 7) by:
  - One-hand Technique (fig. 5) – Hold tubing in hand and advance safety shield with thumb and index finger until the needle is completely retracted and safety shield is locked in place over needle tip, or
  - Two-hand Technique (fig. 6) – Grasp either one wing or both wings with one hand and grip area of the safety shield base with the other hand. Slide the wings back into the rear slot of the safety shield, until the needle is completely retracted and safety shield locked into place over needle tip.
- Safety-Lok™ shield shown locked and protecting needle. (fig. 7).
- Dispose of all properly locked Safety-Lok™ Infusion Sets in appropriate container.







Caution:
Handle all biological samples and "sharps" (lancets, needles, administration sets, luer adapters, blood collection sets, etc.) in accordance with the policies and procedures of your facility. Obtain appropriate medical attention in the event of any exposure to biological samples (e.g., through a puncture injury) since samples may transmit viral hepatitis, HIV (AIDS), or other infectious diseases. Utilize any safety engineered feature if the device provides one. Discard all "sharps" in biohazard containers approved for their disposal.
Always follow Universal Precautions.
Visually confirm that the needle point is completely covered after activation.
After single-use, dispose of product according to your institution's regulations.
R_X Only

Symbol & Mark Key:

- Do Not Reuse
- REF — Catalog Number
- Consult Instructions For Use
- Use By
- LOT — Batch Code
- This End Up
- STERILE EO — Method of Sterilization Using Ethylene Oxide
- Manufacturer
- Keep Away From Sunlight
- Fragile, Handle with Care
- CE Marking